Associations Among Physical Activity, Medication, and Supplement Use and Urinary Sucrose Biomarkers

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Introduction

The typical American diet includes high levels of added sugar as well as low levels of physical activity. The Dietary Guidelines for Americans in 2015 suggest that added sugar intake be limited to less than 10 percent of daily caloric intake to reduce the risk for obesity, cardiovascular diseases, diabetes, and cancer (U.S. Department of Health and Human Services, 2015). In order to identify relationships between added sugar intake and disease, accurate methods for assessing dietary intake of added sugars are needed. Self-reported dietary intake often leads to error and potentially incorrect conclusions (Thompson & Subar 2013). From past research, we know that dietary assessment methods that rely on self-report have disadvantages associated with bias from the respondent, inaccurate food information (intentional or unintentional), and overall, they may not accurately assess their typical diet (Thompson & Subar 2013). Objective biomarkers of added sugar intake could further improve measurement of exposure to added sugars without relying solely on subjective dietary records. Urinary sugar excretion has been proposed as a possible biomarker to detect dietary sucrose and fructose. Research has shown that urinary sugars are a better reflection of extrinsic (added sugars) than intrinsic sugars (natural sugars) based on their differences in digestion and absorption (Tasevska et al. 2009). Another study showed that estimated total sugar intake based on urinary sugar excretion was positively associated with BMI, waist-to-hip ratio, and waist circumference (Campbell et al. 2017). Both studies used a 24-hour urine collection and analyzed the samples with a sucrose, fructose and glucose enzyme kit. A 24-hour urine collection is burdensome to participants, so using a single urine would be the ideal sample for biomarker analysis, but it has its limitations. The European Prospective Investigation into Cancer in Norfolk (EPIC) examined the associations between sugar intake and overweight individuals. The study used a single-urine spot analysis, but urinary sucrose analyses failed for 195 participants and results were outside the calibration range for 1,442 participants which dropped the total sample size from 3,371 to 1,734 individuals (Kuhnle et al. 2015). Based on previous research, there is a need for a biomarker that is valid, reliable, inexpensive, and sensitive to dietary changes to improve measurement of exposure to added sugars.

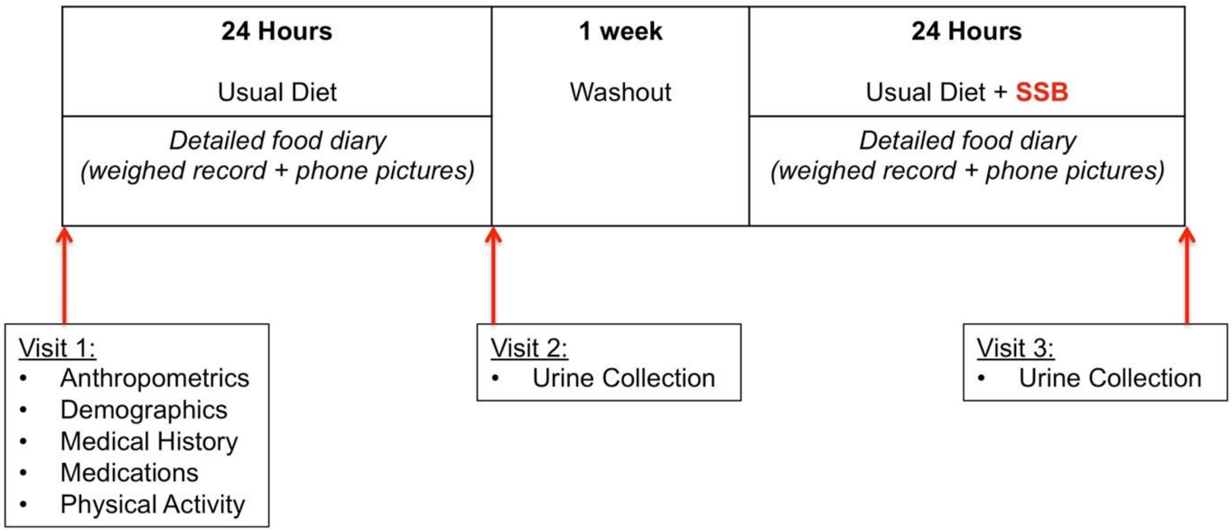
Supplement use among postmenopausal women in the United States has increased significantly in the past 30 years. In 1986, 65.5% reported consuming dietary supplements whereas in 2004, 85.4% reported usage (Park & Jacobs 2009). Multivitamin usage has also increased from 31.7 to 62.5% and calcium from 46 to 60% between 1986-2004. (Park & Jacobs 2009). With an increase in dietary supplement usage among postmenopausal women, it is important to investigate the impact it may have on urinary sucrose excretion. As for medication use, postmenopausal women reporting taking medication in the United States has increased from 52.7% to 69.8% between 1988-2004 (Randhawa et al. 2017). There is an increase in supplement and medication usage with an increase in age whereas physical activity decreases with age. Approximately 51% of women aged 50-54 are meeting or exceeding physical activity recommendations whereas only 37% of women 60 and older are meeting those requirements (Ekenga et al. 2015). Physical activity also differs by race and weight status. Nonhispanic white women are more active than minority women, and women with lower BMI are also more active than those with a higher BMI (Ekenga et al. 2015). In a study by Kim et al., it was found that regular exercise can modify urinary excretion of certain nutrients like riboflavin and thiamin (2015). So, we hypothesized that physical activity may have an impact on urinary sucrose excretion and may influence the validity of the biomarker. The primary objective of this research project was to examine the associations between physical activity and urinary sucrose excretion while secondarily examining the associations among medication and supplement use and urinary sucrose excretion.

Methods

This research project was a part of a larger study, the Added Sugar Biomarker Study (ASBS), that evaluated the associations between dietary sugar intake and urinary sugar excretion among postmenopausal women. ASBS used an experimental pre-post test single group design to test the sensitivity of a urinary sucrose/fructose biomarker in detecting added sugar in the diet. Women were recruited in the Columbus, Ohio area with the use of the website ResearchMatch.com as well as flyers posted around The Ohio State University Columbus campus. Thirty women were enrolled and completed the study. Eligibility included being a postmenopausal female (natural amenorrhea greater than 12 months), 40 years of age or greater, a BMI between 18.5-24.9 kg/m^2 (healthy weight group) or greater than 30kg/m^2 (obese group), having a device capable of taking photographs and being able to take photos and send photos from this device, and understanding English and able to write at the 8th grade level, with the ability to give written, informed consent to participate. Exclusion criteria from this study included a history of diabetes mellitus or prediabetes, renal disease, gastrointestinal disorders, or other conditions that could alter sucrose metabolism or excretion, pregnant or nursing women, and those unable to give informed consent. Interested participants contacted the researcher who read a study script and then orally asked questions for screening of eligibility. If the volunteer was potentially eligible from the results of the telephone screening, she was scheduled for an in-person baseline screening where eligibility was confirmed, and informed consent was obtained. If eligible, the researcher obtained anthropometric measurements, medical history, medication and supplement usage, a measure of normal physical activity (PA) level using the Godin survey (NIH, 1985), and demographic information.

At the baseline visit, the RDN (Registered Dietitian Nutritionist) explained to the participant how to complete a weighed, photographed food record and provided written instructions on completing the food record and collecting fasting urine. Following the instructional baseline visit, two more visits were required for participation in the study. Both of these visits included collection of the 24-hour weighed photographed food record, as detailed previously, and fasting urine collection. Within 7-10 days of the baseline-screening visit, the participant scheduled her first urine collection appointment at the clinic. At this appointment, the participants provided samples from Day 1: one weighed, photographed record of their normal daily intake over the previous 24 hours, and fasting urine was collected from the fast that began at midnight the morning of the clinic visit. First morning urine (collected at home) and a specimen collected in the clinic (termed "clinic urine") were obtained. After the first urine collection visit, the participant was provided with a sugar sweetened tea to consume during her second day of recording a 24-hour weighed, photographed food record. Between the first and second food record/urine collection visit, there was a one-week washout period where participants were instructed to consume their normal diets. On the day of their second food record, participants were asked to consume their normal diet plus the provided sugar-sweetened beverage. The following morning, women collected their second fasting urine sample and brought this to the Orchard lab for their final study visit where clinic urine was obtained and the RDN reviewed and collected the food record (samples from Day 2).

Figure 1. Study Time Line



Physical activity was assessed using the Godin-Shepherd Leisure Time Physical Activity Questionnaire (Godin 1985). Weekly frequencies of physical activity for at least 15 minutes in three levels of leisure time (mild, moderate, strenuous) were used to calculate a total leisure activity score (TLAS). Mild refers to minimal effort, moderate is not exhausting, and strenuous is heart beating rapidly. They also indicated how often during the week they engaged in regular physical activity long enough to work up a sweat (heart beating rapidly). Participants were then classified as low activity (< 14 units), moderate (14 to 23 units), and active (≥ 24 units) based on an equation including the factors mentioned previously.

The medication and supplement inventory questionnaire was modified from the Women's Health Initiative Form 153. Participants indicated whether they were taking any medications that required a prescription from a doctor or healthcare provider and provided the name, strength, medication type, and how long they had been taking the medication. The same information was provided for non-prescription medicines taken at least once in the past two weeks. The participants also indicated vitamin, mineral, or other dietary supplements taken at least once a week in the past two weeks. The participants provided the product name, frequency of intake, and how long they've been taking it. They were asked specific questions in regard to multivitamins, single vitamin/mineral supplements, fish oil, flaxseed/plant oil, or any other herb, botanical or dietary supplements.

Descriptive statistics including means, standard deviations, and frequencies were used to summarize the outcome characteristics of the women who completed the study. Pearson correlations were used to evaluate weekly physical activity, total medications, and total supplements with first morning urinary sucrose excretion. T-tests were used to compare differences between women with healthy weight and women with obesity measures. One-way ANOVA was used to determine statistically significant differences between the medication or supplement category and mean first morning urinary sucrose excretion. All data were analyzed using JMP PRO 14.

Results

Table 1 contains information regarding the characteristics of the study sample. The mean body mass index (BMI) of the participants was 30.7±8.4 kg/m^2, with an average age of 60 ± 5 years, and 93% were white. Women with healthy weight reported taking on average 4 medications regularly while women with obesity reported taking on average 5 medications regularly. Supplement usage was similar with all participants taking an average of 3 dietary supplements regularly. Women with healthy weight had a total leisure activity score (TLAS) of 41.0 ± 29.4 while women with obesity scored 28.7 ± 23.6 with a p-value of 0.22. A higher TLAS indicates higher weekly physical activity.

Table 1: Demographic characteristics

	All Participants (n=30)	Women with Healthy Weight (n=15)	Women with Obesity (n=15)
	Mean (SD)[b]	**Mean (SD)[b]**	**Mean (SD)[b]**
Age (years)	60.0 (5.0)	61.1 (5.26)	58.9 (4.56)
BMI (kg/m^2)[a]	30.7 (8.4)	23.4 (2.04)	37.96 (5.42)
	N (% of total)	**N (% of total)**	**N (% of total)**
Race: Nonhispanic black	2 (6.7)	0 (0)	2 (13.3)
Nonhispanic white	28 (93.3)	15 (100.0)	13 (86.7)
	Mean (SD)[b]	**Mean (SD)[b]**	**Mean (SD)[b]**
Medications Reported	3.9 (3.3)	3.8 (2.96)	5.13 (3.46)
Supplements Reported	2.6 (2.2)	2.93 (1.28)	2.87 (2.85)
Total Leisure Activity Score (TLAS)[c]	34.8 (26.9)	41.0 (29.4)	28.7 (23.6)

[a] Body Mass Index

[b] SD=standard deviation

[c] Total weekly leisure activity score calculated in arbitrary units from Godin-Shephard Leisure-Time Exercise Questionnaire. Score can be interpreted as active (≥24 units), moderately active (14-23 units), or sedentary (<14 units).

Table 2 contains information on medication use by category reported by women with healthy weight and women with obesity. Pain medication was the most frequently used category with 21 out of the 30 women reporting taking at least one. The next two most frequently used medication categories were antidepressants (n=13) and cardiac (n=13) medications. More women with obesity reported taking antihistamines than women with healthy weight, but the trend was not statistically significant (p=0.06).

Table 2. Medication use by category reported by women with healthy weight and women with obesity[a]

Medication Category	Women with Healthy Weight	Women with Obesity	P-value[b]
Antidepressants	7	6	0.92
Antihistamines	1	5	0.06
Cardiac	4	9	0.14
Hormonal	6	4	0.70
Gastrointestinal	5	7	0.54
Neurological	4	4	0.76
Pain	11	10	0.89
Other	2	4	0.54

[a] Number of women who reported taking at least one medication in the category

[b] T tests compared means between women with healthy weight and women with obesity

Table 3 contains information regarding dietary supplement use by category among the 30 post-menopausal women. Supplement use did not differ significantly by weight status. The most frequently reported dietary supplement was Calcium/Vitamin D (n=20) followed by multivitamin usage (n=16) and the other category (n=16). Common supplements found in the other category includes bergamot, black cherry, and cranberry extract.

Table 3. Self-reported dietary supplement use among 30 post-menopausal women

Supplement Category	Women Taking 0	Women Taking 1	Women Taking 2+
B-Vitamins	20	10	0
Calcium/Vitamin D[a]	10	18	2
Fish Oil/Omega 3	23	7	0
Magnesium	26	4	0
Multivitamin	14	16	0
Other	14	9	7

[a] Category includes calcium, vitamin D, and combined calcium + vitamin D supplements

Table 4 contains information regarding weekly physical activity reported by women with healthy weight and women with obesity. Women with healthy weight tended to engage more frequently in moderate and strenuous physical activity (PA) than women with obesity (but trends were not statistically significant; p=0.28 and p=0.15, respectively).

Table 4. Weekly frequency of physical activity reported by women with healthy weight and women with obesity

Weekly Physical Activity Level [a]	Women with Healthy Weight (n=15)	Women with Obesity (n=15)	
	Mean[b] ± SD[d]	Mean[b] ± SD [d]	P-value [c]
Mild	2.76 ± 2.58	3.46 ± 3.68	0.55
Moderate	3.23 ± 3.41	2.03 ± 2.56	0.28
Strenuous	1.9 ± 2.19	0.9 ± 1.46	0.15

[a] Results from Godin-Shepard Leisure Time Physical Activity Questionnaire; Mild = minimal effort; moderate = not exhausting; strenuous = heart beating rapidly

[b] Weekly frequency of engaging in physical activity for at least 15 minutes at each of the three levels of activity (moderate, mild, strenuous)

[c] T tests compared means between women with healthy weight and women with obesity

[d] SD = standard deviation

Table 5 contains information regarding the associations between urinary sucrose excretion and physical activity, medication, and supplement usage. There was a trend for a direct association between fasting first morning urinary sucrose with total supplements reported (not significant, p=0.0667). This trend prompted us to look further into supplement usage by category with urinary sucrose excretion.

Table 5. Associations between urinary sucrose excretion and physical activity, medication and supplement usage

	Urinary Sucrose (ug/mg)	Day 1, Participants with detectable urinary sucrose (n=22)[a]		Day 2, Participants with detectable urinary sucrose (n=23)[a]	
		R	p-value[b]	R	p-value[b]
Total leisure activity score[c]	First Morning Urine	-0.17	0.46	0.17	0.43
Total medications[d]	First Morning Urine	0.1	0.67	0.24	0.27
Total supplements[d]	FIrst Morning Urine	0.19	0.39	0.39	**0.0667**

[a] Detectable urine includes urinary sucrose samples above the limit of detection

[b] Analyses from partial Pearson correlations were used to assess TLAS, medications, and supplements and first morning urinary sucrose

[c] Total weekly leisure activity score calculated in arbitrary units from Godin-Shephard Leisure-Time Exercise Questionnaire. Score can be interpreted as active (≥24 units), moderately active (14-23 units), or sedentary (<14 units).

[d] Total medication and supplement inventory questionnaire was modified from the Women's Health Initiative Form 153

Table 6a and 6b contains information regarding differences in urinary sucrose by supplement usage on day 1 and day 2, respectively. Participants taking B-Vitamin supplements had significantly higher first morning urinary sucrose on Day 1 (p=0.0081) and Day 2 (p=0.0010) compared to participants not taking B-Vitamins. Participants taking a multivitamin supplement had significantly higher first morning urinary sucrose compared to participants taking no multivitamin on Day 1 (p=0.0285) but not on Day 2. Participants taking a magnesium supplement had significantly higher first morning urinary sucrose compared to participants taking no magnesium supplement on Day 2 (p=0.0229), but not Day 1.

Table 6a. Differences in Fasting Urinary Sucrose by Supplement Usage – Day 1[a]

	Women Taking 0	Women Taking 1	Women Taking 2+	
	Urinary Sucrose (ug/mg) Mean±SD[c]	Urinary Sucrose (ug/mg) Mean±SD[c]	Urinary Sucrose (ug/mg) Mean±SD[c]	P-value[b]
B Vitamins	38.81± 22.55	148.71 ± 29.83	-	0.0081
Calcium/Vitamin D	52.4 ± 37.49	91.1 ± 25.61	-	0.4041
Fish Oil/Omega 3s	82.96 ± 24.41	64.6 ± 45.01	-	0.7237
Magnesium	86.67 ± 23.44	43.32 ± 49.72	-	0.4396
Multivitamin	29.54 ± 28.24	119.82 ± 25.78	-	0.0285
Other	67.79 ± 28.25	145.02 ± 48.93	56.63 ± 39.95	0.3390

[a] Sample size = 22

[b] Analyses from Oneway ANOVA were used to assess supplement and mean first morning urinary sucrose excretion

[c] SD = standard deviation

Table 6b. Differences in Fasting Urinary Sucrose by Supplement Usage – Day 2[a]

	Women Taking 0	Women Taking 1	Women Taking 2+	
	Urinary Sucrose (ug/mg) Mean±SD[c]	Urinary Sucrose (ug/mg) Mean±SD[c]	Urinary Sucrose (ug/mg) Mean±SD[c]	P-value[b]
B Vitamins	46.19 ± 13.34	132.3 ± 18.27	-	0.001
Calcium/Vitamin D	46.87 ± 24.21	88.94 ± 16.01	-	0.162
Fish Oil/Omega 3s	80.06 ± 16.21	65.02 ± 27.28	-	0.6405
Magnesium	64.4 ± 13.24	154.39 ± 34.19	-	0.0229
Multivitamin	65.98 ± 21.04	83.95 ± 18.45	-	0.5279
Other	68.88 ± 20.63	83.22 ± 27.94	82.36 ± 27.94	0.8886

[a] Sample size = 23

[b] Analyses from Oneway ANOVA were used to assess supplement and mean first morning urinary sucrose excretion

[c] SD = standard deviation

Discussion and Concluding Statements

In this study, there were no associations between urinary sucrose excretion and physical activity levels. There was a trend for a direct association between total supplements and fasting first morning urinary sucrose on Day 2. Participants taking a b-vitamin, multivitamin, or magnesium regularly had significantly higher first morning urinary sucrose excretions than participants reportedly not taking these supplements. There is no current evidence from existing literature that demonstrates or explains the relationship between urinary sucrose biomarkers and vitamins. The results of this study demonstrated a statistically significant association between dietary supplement usage and urinary sucrose excretion.

The main objective of this project was to examine the relationship between physical activity and urinary sucrose excretion. Literature shows that physical exercise requires a significant amount of energy, and riboflavin and thiamin function as coenzymes for these pathways (Kim et al. 2015). Kim and colleagues found that regular moderate exercise training increased urinary excretion of thiamin (Kim et al. 2015). In the current study, there were no significant relationships between physical activity and urinary sucrose excretion. In another study examining the relationship between vitamin C and glucose, they found that high levels of vitamin C supplementation produced strong false-positive results for the glucose Benedict's test (Brandt et al. 1976). They suspect that vitamin C competes with the chromogen in the glucose test, and the capacity of the ion-exchange resin might be overwhelmed, so it produces a false-positive result (Brandt et al. 1976). In the current study, vitamin supplementation with B vitamin, multivitamins, and magnesium was associated with higher urinary sucrose excretion. While the interaction between urinary sugar excretion and vitamin supplementation is poorly described in the literature, the previously stated results show that there may be a relationship between urinary sugars and dietary supplementation. Clearly, there is a need for additional research into these relationships to further elucidate these findings.

There are several limitations to this study. The small sample size increases margin of error and may make it difficult to find significant relationships from the data. The main objective was to explore the associations between physical activity and urinary sucrose biomarkers. There were no significant associations, but if there was a larger sample size, it would have increased the chances of detecting a significant association if there was indeed such a relationship. Also, the women taking a magnesium supplement had significantly higher first morning urinary sucrose excretion compared to those not taking a magnesium supplement, but this consisted of only 3 women out of the 30, and only on Day 2. Therefore, this association should be interpreted cautiously. It may be difficult to give this finding as much significance or draw a conclusion based on the small sample. The study also included limited diversity. The sample consisted of 28 nonhispanic white women and 2 nonhispanic black women. Black women are disproportionately affected by obesity in the United States with almost two-thirds being considered obese based on BMI (Agyemang & Powell-Wiley 2013), but the sample did not fully represent black women or other minority groups affected disproportionately by obesity and its comorbidities. Finally, although the inclusion criteria included healthy postmenopausal women with no history of diabetes mellitus or prediabetes, women with obesity may have had altered sugar metabolism despite no current diagnosis of diabetes mellitus/prediabetes which could have interfered with urinary sucrose excretion. In a study examining the concentrations of water-soluble vitamins in blood and urinary excretion in patients with diabetes, they found concentrations of vitamins B2, B6, C, niacin, and folate in blood were significantly lower in type II diabetes participants than the controls (Iwakawa et al. 2016). There was evidence of increased urinary clearances of these vitamins, so the lower levels were likely due to impaired reabsorption processes (Iwakawa et al. 2016). The previously stated findings show a relationship between urinary excretion of vitamins and type II diabetes, so it is possible that altered sugar metabolism may interfere with urinary excretion and absorption of nutrients.

In conclusion, physical activity does not seem to contribute to excretion of sucrose in the urine of healthy postmenopausal women. Taking b-vitamins, multivitamins, or magnesium dietary supplements is related to excreting significantly higher amounts of first morning urinary sucrose compared to those not taking the dietary supplements. However, future research in a larger, more diverse sample is needed to confirm this finding and understand the association of urinary sucrose biomarkers and dietary supplements in older women.

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